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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/897,107	07/03/2001	Akihiko Yamagishi	210383US0	9251

22850 7590 12/18/2002

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EXAMINER

RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 12/18/2002

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicant(s)

09/897,107

Applicant(s)

YAMAGISHI, AKIHIKO

Examiner

Delia M. Ramirez

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 September 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-16 is/are pending in the application.
- 4a) Of the above claim(s) 7-10 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6 and 11-16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on _____ is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1-16 are pending.

Applicant's election with traverse of Group I, claims 1-6, 11-16 drawn to a method for improving thermostability of proteins, in Paper No. 11, filed on 9/30/2002 is acknowledged.

Applicant's traverse is on the ground(s) that claims from Group III depend from claims of Group II, which in turn depend from claims of Group I, therefore it is improper to separate these groups. In addition, Applicants argue that the Examiner has not provided sufficient reasons to support the characterization of the different Groups as unrelated. It is Applicant's opinion that the search of all claims would not constitute a serious burden on the Office.

Applicant's arguments have been fully considered but are not deemed persuasive to overcome the restriction requirement. While it is agreed that claims from some groups recite limitations which are defined in claims from other groups, each of the groups is drawn to independent and distinct inventions (i.e. polynucleotide, polypeptide, and method for improving thermostability) for the reasons already stated in previous Office Action Paper No. 10, mailed on 8/29/2002. In regard to the lack of reasons why the claimed inventions are unrelated, while it is the Examiner's contention that the inventions are unrelated, even if one assumes that the protein of Group II and the method of Group I are related as product and method of making the product, such protein can be made by chemical synthesis or isolated from natural sources. Furthermore, as stated in previous Office Action Paper No. 10, the polypeptide of Group II and the polynucleotide of Group III are independent and distinct inventions. In regard to arguments that the claims should be examined together without undue burden, it is noted that a comprehensive

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search of all groups would require a sequence search, patent and non-patented literature searches and a class/subclass search. Furthermore, the searches for all the claimed inventions is not co-extensive.

The requirement is deemed proper and therefore is made FINAL.

Claims 7-10 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Specification

1. The disclosure is objected to because it is replete with improper idiomatic English terms and/or typographical errors. See, for example, page 8, lines 25-26, "mechanism of the realization of the amino acid residue", Table 1, page 17, "ancestralspecies", page 25, line 12, "lager production", page 7, line 7 "molecuar evolutinary", etc. Appropriate correction is required. Applicant should be careful not to introduce new matter in amendments to the specification.

Priority

2. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to Japan application No. 2000-201920 and 2001-164332 filed on 7/4/2000 and 5/31/2001, respectively. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 3/7/2002 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

4. The drawings have been reviewed and are approved by a draftsman under 37 CFR 1.84 or 1.152.

Claim Objections

5. Claim 3 is objected to because of the following informalities: the term "alingment" is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 1-6 and 11-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 1 and 3 (claims 2, 4-6, 11-16 dependent thereon) are indefinite in the recitation of "species which evolutionarily correspond to each other in a phylogenetic tree" as it is unclear

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what the meaning of the term is within the context of the claims. For examination purposes, the term will be interpreted as “any species of a phylogenetic tree”. Correction is required.

9. Claims 1 and 3 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. There is no step connecting the replacement of amino acid residues in step (iii) and improvement of thermostability. It is suggested that the additional steps of claim 2 be added to claim 1 for completeness. Correction is required.

10. Claims 11 and 12 are indefinite in the recitation of “wherein the protein is..” as it is unclear which protein is being referred to. The method of claim 1 refers to a method where many proteins are involved: the proteins being compared, the ancestral protein, and the protein being tested for improved thermostability. It is suggested that if the intended protein is that being tested, the claims be amended accordingly. For examination purposes, it will be assumed that the limitation recited refers to the protein being tested for thermostability. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-6 and 11-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

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convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-6 and 11-16 are directed to a method for improving thermostability of genera of proteins wherein the amino acid sequences of proteins of different functions are compared.

While the specification discloses a method for improving thermostability of a few species of 3-isopropyl malate dehydrogenases by comparison of amino acid sequences of isocitrate dehydrogenases and 3-isopropyl malate dehydrogenases (functional homologs), there is no disclosure of how to improve the thermostability of other proteins, as encompassed by the claims, with the claimed method. Similarly, there is no disclosure of how one can improve thermostability of a protein by comparing amino acid sequences of proteins of different function. While one could argue that the information provided in the specification is sufficient to adequately describe how to improve the thermostability of any protein, it is noted that one of skill in the art would require to know (1) the amino acid sequences of those functional homologs which are required to construct the ancestral protein and (2) some knowledge or guidance as to which proteins can have their thermal stability enhanced since it is not expected that any protein can be thermally stable. The specification discloses practicing the claimed method with amino acid sequences of proteins of similar function to that of the protein being modified and only discloses a single species of the genera of proteins (3-isopropyl malate dehydrogenases) wherein thermostability can be enhanced which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of the claimed method. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

13. Claims 1-6 and 11-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for improving the thermostability of 3-isopropyl malate dehydrogenases wherein amino acid sequences of 3-isopropyl malate dehydrogenases and isocitrate dehydrogenases are compared, does not reasonably provide enablement for a method for improving the thermostability of any protein wherein the amino acid sequences of proteins of different functions are compared. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims.

As indicated above, while the scope of the claims encompasses the improvement of thermostability of any protein by comparison of amino acid sequences of proteins of different functions, the specification discloses a method for improving thermostability of a few species of 3-isopropyl malate dehydrogenases by comparison of amino acid sequences of isocitrate dehydrogenases and 3-isopropyl malate dehydrogenases (similar function). There is no disclosure of how to improve the thermostability of other proteins, as encompassed by the claims, with the claimed method, nor there is disclosure of how one can improve the thermostability of a protein by comparing the amino acid sequences of proteins with different

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function to that of the protein being modified. It is unclear how one of skill in the art can enhance the thermostability of a specific protein by comparing amino acid sequences of proteins of different functions. Furthermore, to improve the thermostability of any protein as claimed, one would require to know (1) the amino acid sequences of those functional homologs which are required to construct the ancestral protein and (2) some knowledge or guidance as to which proteins can have their thermal stability enhanced.

In regard to finding the functional homologs required to construct the ancestral protein, while one could argue that such homologs can be isolated by sequence comparison with proteins of known function, the state of the art teaches the unpredictability of assigning function based on sequence homology. Bork (Genome Research, 10:398-400, 2000) teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* were found to be hydroxylases once tested for activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. Therefore, since the functional homologs may not be available for a specific protein, one of skill in the art may not be able to practice the claimed method.

In regard to determining which proteins can have their thermal stability enhanced, since not all proteins are intended to be functional at high temperatures, it is not expected that the thermal stability of all proteins can be enhanced with the claimed method. Most likely, one of skill in the art would expect the claimed method to enhance the thermostability of those proteins which are isolated from thermophilic organisms or those proteins which have a thermally stable counterpart in nature. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of information as to how one of skill in the art can practice the claimed method using amino acid sequences of proteins of different functions, the lack of knowledge about which proteins can have their thermal stability enhanced, and the unpredictability of the prior art in regard to function based on homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the full scope of the claimed method. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Lehmann et al. (Protein Engineering 13(1):49-57, January 2000; cited in the IDS). Lehmann et al. teaches a method for improving the thermostability of phytases by comparing the amino acid sequences of 13 phytases derived from six fungal species and constructing a consensus phytase (ancestral phytase; page 51, column 2). Lehmann et al. also teaches the testing and selection of the

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consensus phytase (page 51 column 2, page 52, column 1), which shows improved thermostability (page 53, Figure 2). The amino acid sequences were aligned using the PILEUP program (multiple alignment program; page 50, column 2, first paragraph).

Claim 1 is directed to a method for improving thermostability of proteins which comprises the steps of (i) comparing amino acid sequences of proteins from two or more species, (ii) estimating the amino acid sequence of an “ancestral protein”, (iii) comparing the amino acid residues of one of the proteins used in the comparison step with the ancestral protein and replacing one or more amino acids of the protein which are different from those of the ancestral protein with the same amino acid residues as those of the ancestral protein. Claim 3 adds the limitation that the sequences be compared by multiple alignment. Claims 2 and 4 are directed to the methods of claims 1 or 3, respectively, further comprising the steps of testing and selecting a protein with improved thermostability. Claims 5 and 6 are partially directed to the methods of claims 1 or 3, respectively wherein two or more proteins belonging to the same family are included in the comparison method. Since the protein obtained in step (iii) is one where one can replace as many amino acid residues as to obtain the ancestral protein, the consensus phytase of Lehmann et al. is that of step (iii). Also, all the sequences aligned are those of phytases which are all derived from fungal organisms. Therefore, the method of Lehmann et al. anticipate the claims as written.

Conclusion

15. No claim is in condition for allowance.

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16. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.


17. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
December 9, 2002


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